

REMARKS

After entry of this amendment, claims 1-8 and 10-13, and 22-23 are pending. Claims 14-21 have been withdrawn. Claim 9 has been canceled without prejudice to future prosecution. Claims 1 and 12 have been amended to recite that the thrombin substrate comprises a fluorescent label and that the lyophilized mixture comprising CaCl_2 and the thrombin substrate are soluble in water. Support for these amendments is found in claim 9 as filed and in the specification at page 9, paragraph 28. Thus, no new matter is added by these amendments. Claims 1-10 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,124,110 to Wober *et al.* in view of U.S. Patent No. 5,625,036 to Hawkins *et al.*; Lawson *et al.*, *J. Biol. Chem.* 267(7):4834-4843 (1992); Varadi *et al.*, *J. Thrombosis and Haemostasis* 1:2374-2380 (2003); U.S. Patent No. 5,952,198 to Chan *et al.* U.S. Patent No. 6,074,826 to Hogan *et al.*; U.S. Patent No. 6,576,422 to Weinstein *et al.*; and U.S. Patent No. 6,756,019 to Dubrow *et al.* Applicants respectfully traverse this rejection.

Applicants note that claims 11-13 and 22-23 are not specifically addressed in the Office Action, but to the extent that the rejection of claims 1-10 applies to these claims, the rejection is traversed.

As set forth in M.P.E.P. § 2143, [t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The present invention is directed to a kit comprising the following components: (1) a lyophilized tissue factor (TF)/phospholipid (PL)-complex; and (2) a lyophilized mixture comprising CaCl_2 and a thrombin substrate comprising a fluorescent label. Addition of an

aqueous solution to the lyophilized mixture leads to formation of a clear, precipitate-free solution.

Applicants assert that the presently claimed invention is not obvious in view of the cited art for at least the following reason: the combination of references does not teach or suggest a lyophilized mixture comprising CaCl_2 and a thrombin substrate comprising a fluorescent label. Accordingly, the combination of references does not teach or suggest every element of the present claims. Even if one of skill in the art were to modify the cited references, there would be no reasonable expectation of success in generating a lyophilized mixture comprising CaCl_2 and a thrombin substrate comprising a fluorescent label, wherein the mixture forms a clear solution when dissolved in an aqueous solution.

In making this rejection, the Examiner acknowledges that Wober *et al.* does not disclose or suggest a fluorescent substrate, but alleges that Wober *et al.* discloses a dry chromogenic substrate (*see*, Office Action at page 5), that Varadi *et al.* and Lawson *et al.* each disclose a dry, powdered fluorescent substrate that contains a fluorescent label, and concludes that a lyophilized mixture comprising CaCl_2 and a thrombin substrate is obvious in view of the cited references.

There is no hint or suggestion in any of Wober *et al.*, Varadi *et al.* or Lawson *et al.* that the substrates are dried as a mixture with CaCl_2 . The substrates and CaCl_2 are distinct components of the reactions described in each of these references (*see, e.g.*, Wober *et al.* at col. 4, line 47 to col. 5, line 40; Varadi *et al.* at page 2375, second full paragraph; and Lawson *et al.* at page 4836, col. 2, third full paragraph). As explained in the instant specification, addition of CaCl_2 to a fluorescent substrate leads to formation of a precipitate (*see, e.g.*, page 9, paragraph 28 to page 10, paragraph 29). Thus, one of skill in the art would not expect that a lyophilized mixture of CaCl_2 and a fluorescent substrate could be dissolved in an aqueous solution to form a clear solution.

Moreover, a dry, powdered substrate is *not* a lyophilized substrate. The fluorescent substrates disclosed in Varadi *et al.* and Lawson *et al.* are dried, but not lyophilized (*see, e.g.*, Lawson *et al.* at page 4836, col. 1, last full paragraph). Lyophilization can substantially alter the properties of a starting material. Therefore, one of skill in the art would

not be motivated to lyophilize the fluorescent substrates disclosed in Varadi *et al.* or Lawson *et al.* alone or as a mixture with CaCl_2 .

In addition, fluorescent substrates are not soluble in aqueous solutions. As set explicitly set forth in Lawson *et al.*, the fluorescent substrate must first be dissolved in DMSO prior to use (*see, e.g.*, page 4836, col. 2, second full paragraph). Thus, in even further contrast to lyophilized mixture recited in the present claims, the substrates of Varadi *et al.* and Lawson *et al.* are not soluble in an aqueous solution.

None of the other cited references, *i.e.*, Hawkins *et al.*, Chan *et al.*, Hogan *et al.*, Weinstein *et al.*, or Dubrow *et al.* remedy the defects in the combination of Wober *et al.*, Varadi *et al.* and Lawson *et al.* because none of the references teach or suggest a lyophilized mixture comprising CaCl_2 and a thrombin substrate comprising a fluorescent label or that such a mixture could be dissolved in an aqueous solution to form a clear solution.

In view of the foregoing remarks, Applicants submit that a *prima facie* case of obviousness has not been established and the presently claimed invention is nonobvious and thus patentable over the cited references. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. §103.

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Amdt. dated December 28, 2005
Reply to Office Action of August 1, 2005


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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 925-472-5000.

Respectfully submitted,


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